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Below please find the final report for the grant R40MC07660 Brown University: **Maternal smoking during pregnancy and infantile GI dysregulation: The case of colic**. Per your emailed recommendations this report includes the following sections: 1) introduction; 2) Review of the literature; 3) Study design and methods; 4) Findings; 5) Discussion. Sections 1-4 are based on our original submission to HRSA.

1) Introduction

A. Nature of the research problem

Infants' healthy growth and development is, in part, predicated on regular functioning of their gastrointestinal (GI) tract. In their first six months of life infants tend to double their birth weight, and their food intake is correspondingly high [1]. Consequently, the GI tract needs to function optimally during this period of intense growth. Identifying prenatal *and* modifiable risk(s) for GI tract dysregulation is important for understanding pathophysiology of such dysregulation, identifying effective and efficient interventions, and most importantly early prevention and health promotion strategies [2].

Such strategies may include preventing mothers from smoking during pregnancy, and ensuring that infants are not exposed to environmental tobacco smoke. As will be outlined below exposure to tobacco smoke is associated with a number of GI problems including colic (e.g., [3]), and reflux [4]. Moreover, in the U.S. alone, nearly half of all women smokers continue to smoke through their pregnancies [5]; this amounts to about 12% of all women who give birth [6] and over half million infants who are annually exposed to cigarette smoke prenatally. If a reduced rate of GI dysfunction among offspring is one of the many anticipated benefits of quitting smoking during pregnancy, in addition to important public health benefits, this information can provide strong additional incentive for pregnant women to quit smoking.

The evidence linking exposure to tobacco smoke with GI dysfunction is most developed for colic. Colic, a syndrome of paroxysms of irritability, inconsolable crying and screaming, is highly prevalent, and is one of the most disruptive manifestations of GI tract dysregulation. Colic's long term sequalae include behavior problems at age 3 ½ [7], sleep problems both during the colic period and after the colic has resolved [8] [9], and feeding difficulties [10-12].

Colic is also distressing for the caretaker. Caretakers of infants with colic have been reported as depressed [13], exhausted [14], and angry [15]. Furthermore, to the extent that mothers of colicky infants provide fewer positive responses to their infants relative to the mothers of non-colicky infants [16, 17], colic may hinder mother child attachment with long-term consequences for both the mother and the infant [18].

Epidemiologic evidence suggests exposure to cigarette smoke or its metabolites is linked with risk of infantile colic (IC). Moreover, recent studies of the gastrointestinal system provide strong, but indirect, corroborating evidence by suggesting physiological mechanisms linking maternal smoking with the offspring's colic. This physiological evidence can be outlined as follows: 1) smoking is linked with increased levels of plasma and intestinal Motilin, and 2)

higher than average levels of motilin are linked with elevated risk of IC. Although these findings from disparate fields provide a cohesive hypothesis for the physiological mechanism linking maternal smoking with IC and other GI disorders, the entire chain of events has not yet been examined among a single cohort, nor has the link between maternal smoking and IC been replicated in a study that simultaneously considers all sources of pre and perinatal exposure to tobacco smoke.

B. Purpose of the investigation.

We examined three hypotheses:

I. In utero exposure (IUE) to cigarette smoke and its metabolites predicts elevated risk of IC.

II. Infants, IUE to cigarette smoke and its metabolites predicts elevated plasma motilin levels.

III. Infants' motilin level predicts their risk of IC.

2) Review of the Literature.

Infantile colic. Infantile Colic is a syndrome of paroxysms of irritability, inconsolable crying and screaming [19]. Its diagnosis is commonly based on Wessel's [20] "rule of threes", which requires the syndrome to persist for: 1) three or more hours a day, 2) three or more days a week, and 3) three or more weeks. IC onsets soon after birth and peaks at 5-8 weeks of age; if left untreated it usually resolves spontaneously by four months of age. Among newborns in Western countries the prevalence of colic is estimated to be between 5 - 28% [21].

Incidence of IC has been attributed to a number of psychosocial factors including infants' difficult temperament or maternal depression and anxiety (e.g., [22]), but none of these associations have been empirically supported [19]. Moreover, in cases of maternal depression and anxiety, any association may be due to the effect of the colicky infant on the mother, rather than colic being a consequence of the mother's depression or anxiety. In his classic study, Illingworth [23] found incidence of colic to be independent of mother's age, parity, pregnancy history, as well as infant's sex, weight, feeding habits, allergies or weight gain. In self-reported studies of colic, or colicky behavior, odds of reporting IC were slightly higher in infants with older, better educated and more affluent parents [24]. This, however, may be a reporting bias where younger and single women would be reluctant to report problems for fear of appearing incompetent. Type of feeding (i.e., breast feeding versus bottle-feeding) has been reported to correlate with colic. However, the evidence regarding which type of feeding may be positively associated with IC is contradictory (e.g., [23-25]).

Gastrointestinal Activity in Humans & Motilin. Gastrointestinal activity in humans consists of two major contractile states: 1) the digestive, and 2) the interdigestive states [26]. In the digestive state sporadic, repetitive contractions occurring simultaneously at all levels of the intestine, mix and churn the nutrients with secretions and repeatedly present nutrients to the

gastrointestinal mucosa. The interdigestive or fasting state is characterized by the migrating motor complex (MMC), which consists of three phases culminating in a series of intense phasic contractions lasting about 5 minutes (phase III). This is followed by a 15-60 minute period with little or no contractile activity (phase I), and then by a 15-60 minute period of intermittent and irregular contractions (Phase II). Phase II leads to another phase III contractile wave that completes the MMC cycle [27].

Motilin, a 22-amino acid hormone is present throughout the gastrointestinal (GI) tract of humans and other species [28]. Intravenous infusion of gastrointestinal hormone motilin induces Phase III activity [26]. In particular, motilin stimulates gastric and intestinal motility by inducing interdigestive phase III antrum and duodenal MMC[29]. Motilin's only known function is initiation of the MMC [30].

Motilin is released cyclically every 90 minutes in the fasting state. The highest plasma motilin levels are seen during fasting when the average adult level is 72 +/-6pmol/L but individual levels vary over a wide range[31]. Gut hormones are present early in fetal development and adult patterns of motilin distribution in the GI tract are evident by 20 weeks of gestation. Fetal plasma motilin levels are approximately 60% of maternal levels by 18-22 weeks of gestation. However, MMC is seldom seen prior to 32 weeks of gestational age suggesting that motilin receptor cells have not matured until late in the third trimester. Motilin levels in infancy are much higher than adult levels with average preprandial levels reaching 172 +/- 33 pmol/L and an average postprandial trough of 68 +/- 12 pmol/L by day 13 and decreasing with age [32]. Serum levels also differ by feeding type. Average basal serum motilin levels are higher for formula fed infants compared to breast-fed infants, 65 +/- 44 pmol/ml versus 32 +/- 8 pmol/ml [25].

Evidence of a Link between Maternal Smoking and IC. To date, seven studies have examined the link between parental smoking and IC. Six of these studies have focused on maternal smoking during lactation, and five of these studies have found a positive association between maternal smoking during lactation and IC. To date only one study has examined the effect of maternal smoking *during* pregnancy on the risk of IC. Below we briefly review these seven studies.

Two small cross-sectional studies showed an elevated risk of IC when the mother smoked during lactation [33, 34] - findings of these two authors are reported based on reviews by Sondergaard, et al., [3]. In a cross-sectional study of 253 infants examined at routine pediatric consultation at 3 months of age, postprandial IC, defined in this study as 'regular crying with pain' following feeding, was associated with parental smoking. However, no association was found between parental smoking and evening colic [35].

In another cross-sectional study, a random sample of 16% of the women giving birth in Norway in 1985 (N=885) reported their postpartum smoking habits, breast feeding, infant disorders and demographic characteristics [36]. Forty percent of infants breastfed by mothers who smoked five or more cigarettes per day exhibited colicky symptoms, in this case defined as 'excessive crying

for more than 2-3 hours per day at least 4 days a week', compared with 26% of the children of non-smokers. However, bottle-fed infants were not influenced by maternal smoking.

In a third cross-sectional study a possible connection between 'colic-like' syndrome and smoking was examined among a convenience sample of 42 [37]. Home nurse visitors judged babies to be colicky or to have been colicky during the "preceding few months" based on a list of colic symptoms provided by the investigators that included: crying when all basic needs are met, continuous crying for extended periods or inconsolable crying. Parents of these babies completed reported the number of cigarettes smoked in the home but no other confounding variables were included in the analyses. No association was found between the number of cigarettes smoked at home and colic-like behavior. The small sample size and poor assessment of symptoms make these findings suspect.

In a population-based retrospective study, 3,345 mothers answered a questionnaire on smoking and other predictors of colic. Compared to infants of nonsmokers, infants of mothers who smoked at least 15 cigarettes were twice as likely to have colic, defined, and based on Wessel's criteria, as 'crying for more than three hours a day on more than 3 days' for the week preceding the interview [38]

Finally, the association between maternal smoking during pregnancy and IC was examined in a prospective study of 1,820 mothers and their infants. In the self-administered questionnaires colic was defined as 'several hours of crying per day for several days with legs drawn up toward the abdomen, distended abdomen and excessive flatus.' For health visitors colic was defined as "at least 3 hours of crying per day for at least 3 days per week for more than 3 weeks or more than 1.5 hours of crying per day in 6 out of 7 days and included the characteristic behaviors of drawn up legs, abdominal distention and excessive flatus". Compared to infants of non-smokers, infants of mothers who smoked at least 15 cigarettes during pregnancy had a two-fold increase in their risk of IC. Infants of mothers who smoked postpartum were also twice as likely to have colic. Surprisingly, infants of mothers who smoked both during pregnancy and postpartum were only 50% more likely to have colic compared to infants of non-smokers [3].

In sum, despite the lack of a standard definition for IC across the studies, there appears to be a link between maternal smoking and IC. With one exception these studies strongly suggest this link to be independent of feeding type.

The Physiological link between maternal smoking and IC. The physiological evidence implicating motilin as a causal agent can be outlined as follows: 1) smoking is linked with elevated motilin levels, and 2) elevated motilin levels are associated with higher risk of IC. Below we detail the evidence for these two links.

Exposure to tobacco metabolites is linked with elevated plasma motilin levels. Two studies have examined the effect of smoking on serum motilin; both have found a positive association between smoking and plasma motilin levels. In a study by Bell et al., [39] heavy smokers, during the course of 1 hour, smoked either 4 high-nicotine cigarettes or 4 low-nicotine cigarettes.

Smoking high-nicotine cigarettes, compared with low-nicotine cigarettes, resulted in significantly higher motilin levels and also in shortening of phase I and II of MMC. In a second study designed to determine whether high motilin levels are related to smoking habit or only to acute nicotine exposure, serum motilin concentration of fasting smokers who abstained from smoking for at least ten hours was compared with serum motilin levels of fasting non-smokers. Smokers had significantly higher motilin levels than non-smokers [40]. Moreover, smoking appears to have both acute and chronic effects on motilin levels.

High intestinal motilin levels are linked with higher risk of colic.

Colicky infants have higher serum motilin levels than infants without colic. In a hospital-based case-control study Lothe examined serum levels of three gut hormones motilin, gastrin, and vasoactive intestinal peptide. Cases were 40 infants with colic, controls were 42 healthy age-matched infants. Lothe found that: 1) formula fed infants, irrespective of colic status, had higher serum motilin levels than breast-fed infants, and 2) infants with colic had significantly higher serum motilin levels than their similarly fed controls, 3) vasoactive intestinal peptide and gastrin levels were not elevated, suggesting some specificity with regards to the role of motilin.

In a prospective study of 78 infants born during one month in 1986 at a Swedish hospital[25], motilin levels were elevated both in cord blood and in blood from neonates who developed colic regardless of whether they were bottle or breastfed. Moreover, there were no differences between motilin levels of mothers of colicky infants and mothers of infants without colic. The authors speculated that the increased motilin levels are "caused by an affectation of the gut present already at birth".

In sum, evidence suggests that infants with colic have higher motilin levels independent of feeding type. Considering that tobacco smoke and its metabolites are present in utero, and can readily reach the infants' blood, the evidence suggests that maternal smoking can increase infant's motilin levels.

3) Study design and Methods

Study design

The study was a prospective cohort with 1(smoker):2(nonsmoker) sampling.

Population studied / Sample selection

Study participants were recruited from the post-partum floor at the Women and Infant's Hospital in Providence, Rhode Island. Participants were recruited based on their smoking status. Eligible participants were at least 18 years of age, spoke English, and signed the consent form approved by the IRB. Characteristics of the study sample are detailed in Table 1.

Table 1 Characteristics of mother-baby pairs, by maternal smoking during pregnancy

Characteristic variable	All sample		Maternal smoking during pregnancy §						
			Never (N=256)		Moderate (N=101)		Heavy (N=43)		
	n	%	n	%	n	%	n	%	p-value¶
Baby characteristic									
Sex									
Male	212	53.0	133	52.0	59	58.4	20	46.5	0.363
Female	188	47.0	123	48.1	42	41.6	23	53.5	
Gestational age (weeks)									
<37	1	0.3	0	0.0	1	1.1	0	0.0	0.221
37-42	360	90.0	231	100.0	89	98.9	40	100.0	
Unknown	39	9.8							
Mean (SD)	39.1	1.2	39.2	1.1	38.8	1.3	39.1	1.0	0.022
Birth weight (grams)									
<2,500	3	0.8	1	0.4	0	0.0	2	4.9	
2,500-4,000	351	87.8	221	86.7	92	93.9	38	92.7	0.009
>4,000	40	10.0	33	12.9	6	6.1	1	2.4	
Unknown	6	1.5							
Mean (SD)	3415.6	451.8	3503.7	436.4	3286.0	448.4	3177.0	399.4	<.0001
Feeding type									
Only breast-fed	65	16.3	61	25.2	2	2.1	2	4.8	
Breast-fed and bottle-fed	88	22.0	69	28.5	12	12.8	7	16.7	<.0001
Only bottle-fed	225	56.3	112	46.3	80	85.1	33	78.6	
Unknown	22	5.5							
Crying									
Excessive crying†	72	18	36	14.1	19	18.8	17	39.5	<.0001
Colic‡	33	8.3	18	7.0	8	7.9	7	16.3	0.124
Maternal characteristic									
Age (years)									
24 or younger	101	25.3	44	17.4	43	42.6	14	32.6	
25 to 29	115	28.8	75	29.6	27	26.7	13	30.2	<.0001
30 to 34	95	23.8	67	26.5	21	20.8	7	16.3	
35 or older	86	21.5	67	26.5	10	9.9	9	20.9	
Unknown	3	0.8							
Mean (SD)	29.0	5.9	29.9	5.8	26.8	5.3	28.1	5.9	<.0001
Race									
White	285	71.3	172	67.5	76	75.3	37	86.1	0.027
Non-white	114	28.5	83	32.6	25	24.8	6	14.0	
Unknown	1	0.3							

Characteristic variable	All sample		Maternal smoking during pregnancy §						
			Never (N=256)		Moderate (N=101)		Heavy (N=43)		
	n	%	n	%	n	%	n	%	p-value¶
Marital status									
Single/Div/Sep/Wid	147	36.8	68	26.6	55	54.5	24	55.8	<.0001
Married/Engaged	253	63.3	188	73.4	46	45.5	19	44.2	
Birth place									
USA	332	83.0	197	77.0	93	92.1	42	97.7	<.0001
Other	68	17.0	59	23.1	8	7.9	1	2.3	
Education level									
High school or lower	167	41.8	77	30.1	69	68.3	21	48.8	<.0001
Some college or higher	233	58.3	179	69.9	32	31.7	22	51.2	
Social support									
No social support	26	6.5	17	7.1	7	7.5	2	4.8	
Support from baby's father	291	72.8	191	79.3	71	75.5	29	69.1	0.347
Support from others	60	15.0	33	13.7	16	17.0	11	26.2	
Unknown	23	5.8							
Erythromycin use during pregnancy	12	3.0	5	2.0	5	5.0	2	4.7	0.191
Caffeine use during pregnancy	392	98.0	248	96.9	101	100.0	43	100.0	0.128
Vitamin use									
Three months before pregnancy	75	18.8	66	25.8	8	7.9	2	4.7	<.0001
1st trimester	334	83.5	225	87.9	75	74.3	34	79.1	0.005
2nd trimester	343	85.8	229	89.5	78	77.2	36	83.7	0.011
3rd trimester	333	83.3	225	87.9	73	72.3	35	81.4	0.002
Active cigarette smoking									
Smoking during pregnancy									
1st trimester	139	34.8							
2nd trimester	118	29.5							
3rd trimester	119	29.8							
Smoking after delivery	123	30.8							
Secondhand smoke exposure									
Expousre during pregnancy									
1st trimester	135	33.8							
2nd trimester	135	33.8							
3rd trimester	142	35.5							
Exposure after delivery (baby)	177	44.3							

* the sum of numbers may be less than 400, due to missing data on some characteristics.

† Excessive crying is defined as "crying ≥ 3 hours per day, and ≥ 3 days per week".

‡ Colic is defined as "crying ≥ 3 hours per day, ≥ 3 days per week, and ≥ 3 consecutive weeks".

Characteristic variable	All sample		Maternal smoking during pregnancy §						
			Never (N=256)		Moderate (N=101)		Heavy (N=43)		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	p-value¶

§ Maternal smoking status during pregnancy is defined by the maximum # of cigarettes per day:
never smoking (0), moderate smoking (1-10), and heavy smoking (>10)

¶ Chi-square test or Fisher exact test for categorical variables, ANOVA for continuous variables.

Instruments used

The study included two interviews: 1) a baseline interview was conducted at the Women and Infant's hospital in Providence, RI, and 2) a follow-up interview was conducted at the participant's home.

Interviews – Participants were queried about their age and smoking status. Qualifying women were presented the informed consent form. A subsample of participants selected at random received an additional visit during which an ETS monitor was placed in a common area in the home and next to the newborn's crib. These data were used to validate data from the questionnaires.

Colic was diagnosed with Colic Symptom Checklist - Lester and colleagues developed the Colic Symptom Checklist [41, 42] to measure the severity of colic.

Maternal smoking was assessed with an instrument based on the Lifetime Smoking Patterns Interview, but modified to focus on the nine months prior to the birth of the index infant [43, 44].

Environmental Tobacco Smoke (ETS) exposure was assessed with passive nicotine monitors placed in the home [45, 46]. These monitors use nicotine as a tracer for ETS exposure, a technique that has been validated across a variety of studies [47].

We administered self-report measures in combination with passive monitors. Our self-report measure of ETS was based on a valid and reliable structured interview that is designed to elicit reliable memory-based reports (90). We assessed the total, average, least and greatest number of cigarettes smoked in the home, in the car/bus and away from home. This self-report measure is highly correlated with objective biomarkers of ETS exposure [48-50].

Feeding time, type and content. Mothers reported time of their infant's last feeding. For bottle fed babies, we ascertained the average number of ounces of milk or formula consumed by the baby during each feeding.

Parenting Stress was assessed by the Parenting Stress Index, a 36-item questionnaire.

Mother and infants' health status and GI problems. Participants completed a current symptom checklist for themselves and their infants. They also completed a section on GI problems.

Statistical methods

Statistical analyses followed the study's aims.

Aim 1. Examine the association between maternal smoking and infantile colic. Odds ratios and 95% confidence intervals were computed. Multivariable logistic regression models were fit following standard modeling guidelines [51]. Mother's and infant's motilin levels will not be

considered in these analyses.

We analyzed quantitative indicators of infant's *in utero* exposure to tobacco smoke (e.g., average number of cigarettes smoked daily by the mother during her pregnancy), using a similar approach as for the main analysis. These secondary analyses will help us evaluate potential dose-response between maternal smoking and incidence of infantile colic. Finally, we will consider continuous outcome variables (e.g., average duration of crying per day). We will model such measures of colic symptom severity as a function of predictors using linear regression.

Aim 2. We will also evaluate the association between maternal smoking and the infant's motilin levels via Multivariable linear regression [52]. If the normality assumption is violated, we will attempt simple transformations before performing t-tests and linear regression modeling. If these are still inadequate, non-parametric methods will be used (Wilcoxon test and median regression).

Aim 3. We will build on and extend the analyses for Aim 1, by evaluating the association between the mother's and the infant's motilin levels and infantile colic. Multivariable analyses will again be carried out via logistic regression. We will follow the same approach as the one used for Aim 1, but motilin levels of the mother and the infant will also be considered as possible predictors of infantile colic.

IV. Findings

Compared to infants who were not exposed to secondhand smoke, infants exposed to secondhand smoke from more 11+ cigarettes per day were 3.6 (95% CI: 1.8, 7.2) times more likely to cry excessively. Moreover, infants exposed to secondhand smoke from more 11+ cigarettes per day were 2.5 (95% CI: 1.00, 6.40) times more likely to have colic. These associations were independent of other previously identified risks of excessive crying (Table 2). We are currently working on the manuscript for this study.

Table 2 Association between maternal smoking during pregnancy and the risk of excessive crying and colic

	Excessive crying† (n=455)			Colic‡ (n=455)		
Characteristic variable	**OR**	**95% CI**		**OR**	**95% CI**	
Baby characteristic						
Baby sex						
Male	Reference			Reference		
Female	0.84	0.52	1.38	0.63	0.32	1.26
Maternal characteristic						
Maternal smoking during pregnancy*						
Never smoking	Reference			Reference		
Moderate smoking	1.46	0.78	2.73	1.12	0.46	2.73
Heavy smoking	3.57	1.76	7.24	2.53	1.00	6.40
Age						
24ys or younger	Reference			Reference		
25 to 29ys	1.07	0.56	2.05	3.16	1.18	8.51
30 to 34ys	0.89	0.41	1.94	2.86	0.90	9.14
35ys or older	1.09	0.49	2.44	5.36	1.72	16.69
Race						
White	Reference			Reference		
Non-white	0.91	0.50	1.65	0.76	0.33	1.76
Maternal marital status						
Single/Div/Sep/Wid	Reference			Reference		
Married/Engaged	0.61	0.34	1.10	0.36	0.16	0.82
Education level						
High school or lower	Reference			Reference		
Some college or higher	1.17	0.66	2.11	0.87	0.39	1.93
Vitamin use during pregnancy (ever vs. never)	1.11	0.47	2.61	0.99	0.31	3.15

OR, odds ratio; CI, confidence interval.

Maternal smoking status during pregnancy is defined by the maximum # of cigarettes per day: never smoking (0), moderate smoking (1-10), and heavy smoking (>10).

Excessive crying is defined as "crying ≥ 3 hours per day, and ≥ 3 days per week".

Colic is defined as "crying ≥ 3 hours per day, ≥ 3 days per week, and ≥ 3 consecutive weeks".

V. Discussion

Evidence from our prospective study suggests an independent link between exposure to maternal smoking during pregnancy and risk of colic. This association is independent of a number of key confounders of the association between maternal characteristics and risk of colic.

Among the strengths of this study is its prospective design. Colic was diagnosed based on Wessel's criteria. We inquired about objective criteria, such as the number of hours the child cries on any given day. By asking for objective information, without reference to colic, we lessened the likelihood of reporting of socially desirable responses. We also assessed a number of potential confounders which to date have not been assessed in any of the studies of maternal smoking and risk of colic. These variables included maternal history of GI problems and infantile reflux, and maternal stress and mood.

Infants' healthy growth and development are predicated, in part, on regular functioning of the gastrointestinal (GI) tract. In the first six months of life infants typically double their birth weight. During this period of intense growth, the GI tract needs to function optimally. Identifying modifiable precursors for GI tract dysregulation is important for understanding pathophysiology of such dysregulation, for identifying effective and efficient interventions, and most importantly for early prevention and health promotion strategies. Findings from out study suggests that one such modifiable precursor appears to be gestational and infantile passive smoking. Colic in infancy has potentially long lasting effects on both the mother child dyad and the entire family. So, reducing risk of colic is likely to have secondary benefits throughout the lifespan.

Finally, we are also pleased to report that, to date, HRSA's support has resulted in the publication of 3 manuscripts in prestigious journals and 2 book chapters.

Morello-Frosh R, **Shenassa ED**. The environmental 'riskscape' and social inequality: Implications for explaining maternal and child health disparities. *Environ Health Perspect*. 2006;114(8): 1150-1153.

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Book Chapters:

Shenassa ED, Brown MJ. Evidence of a link between passive smoking during gestation or infancy and colic. In Jeorgense, NA, ed. *Passive smoke and Health Research.* Nova Science Publishers, Inc. Hauppauge, NY. 2007: 267-282.

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This list will surely grow as we proceed with our work with these data.

With sincere gratitude for your support throughout the years it took to conduct this study.

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